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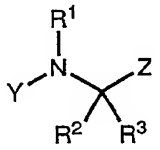
(52) UK CL (Edition L)
C2C CAA CKK C1382 C1530 C215 C246 C247 C25Y C250 C251 C254 C256 C271 C28X C280 C30Y C34Y C342 C366 C368 C385 C51X C511 C537 C584 C62X C628 C65X C658 C80Y C802 U1S S1317 S1318 S1321 S2411 S2415 S2416

(56) Documents cited
US 4992455 A US 4987132 A
Glycine, alanine, valine & leucine

(58) Field of search
UK CL (Edition L) C2C CKK CSJ
INT CL[5] C07D
Online databases: CAS-ONLINE

(54) Nitrogen heterocycle PAF-receptor antagonists

(57) Compounds of general formula I:



(I)

[wherein R^1, R^2, R^3, Y & Z are as defined in claim 1]

and their pharmaceutically and veterinarily acceptable acid addition salts and hydrates are **antagonists of platelet activating factor** (PAF) and as such are useful in the treatment or amelioration of various diseases or disorders mediated by PAF.

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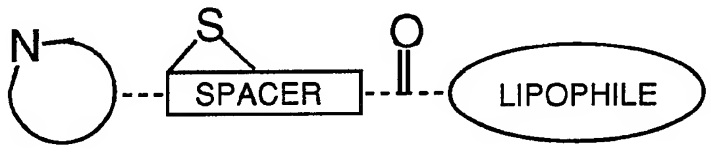
NITROGEN HETEROCYCLE PAF-RECEPTOR ANTAGONISTS

This invention relates primarily to novel compounds which are antagonists of Platelet Activating Factor (PAF).

Platelet activating factor (PAF) is a bioactive phospholipid which has been identified as 1-O-hexadecyl/octadecyl-2-acetyl-sn-glyceryl-3-phosphoryl choline. PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such disorders including asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, cerebral, myocardial and renal ischemia. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of PAF, should be of value in the treatment of any of the above conditions and any other conditions in which PAF is implicated (e.g. embryo implantation).

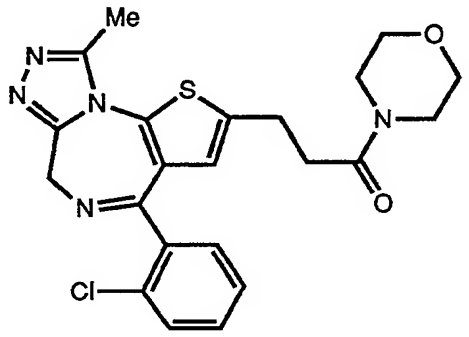
The wide range of compounds which have been disclosed as possessing activity as PAF antagonists have been catagorised into four classes (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)). Certain members of the "heterocyclic sp2 nitrogen class" may be described by the following schematic representation:



The structural features that are important for activity, that are present in most of these compounds, are an sp2 nitrogen heterocycle that is appended to a sulphur heterocycle, a carbonyl or sulphonyl functional group, and a relatively "lipophilic" group. A recent molecular modeling study suggests that the correct relative spatial orientation of these groupings is important for activity (Hodgkin,

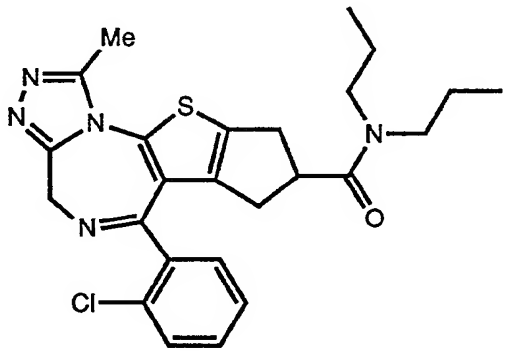
E.E., Bioorg. Med. Chem. Lett., 2(6), 597-602 (1992) Examples of compounds that possess these structural features are as follows:

hetrazepine PAF antagonists such as



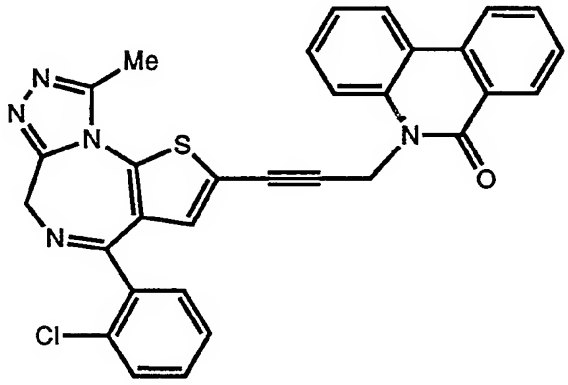
are described by Weber and Heuer (Weber, K.H., Heuer, H.O., Medicinal Res. Rev. 9, 181-218 (1989));

hetrazepine PAF antagonists such as



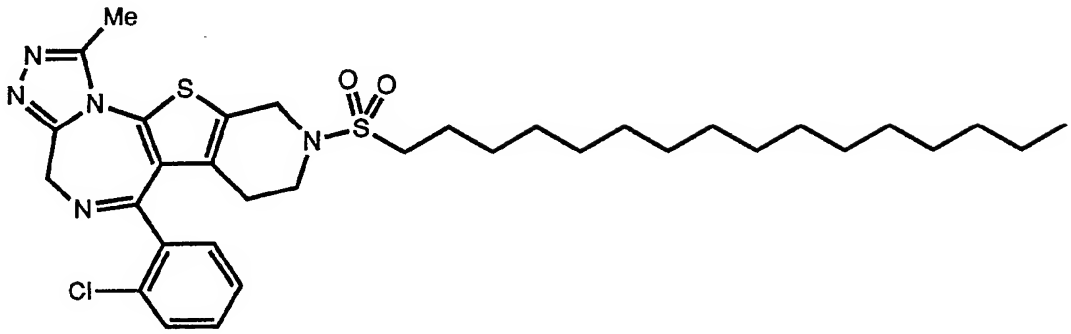
are disclosed in EP-388789-A;

hetrazepine PAF antagonists such as



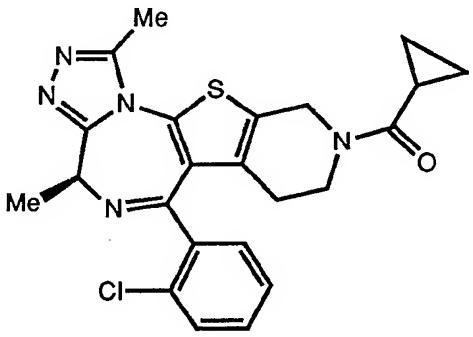
are disclosed in EP-320992-A;

hetrazepine PAF antagonists such as



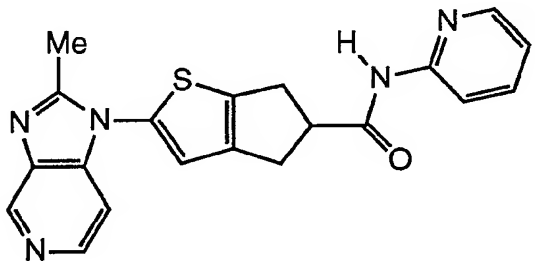
are disclosed in GB2229724-A;

hetrazepine PAF antagonists such as



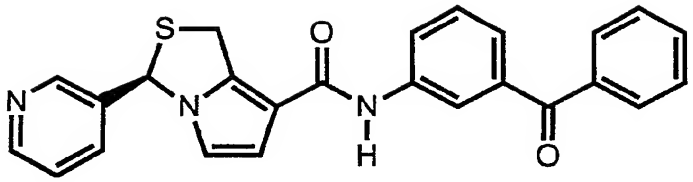
are disclosed in EP-367110-A;

imidazo[4,5-c]pyridin-1-yl PAF antagonists such as



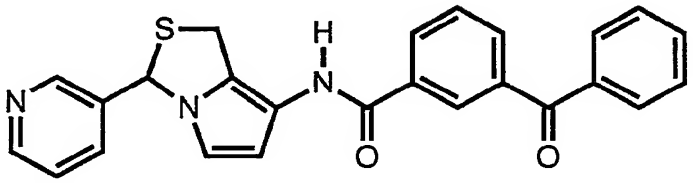
are disclosed in WO9203434;

pyridyl PAF antagonists such as



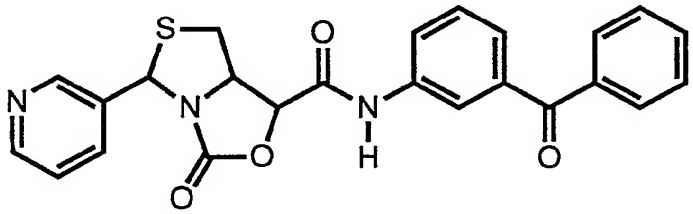
are disclosed in US4783472;

pyridyl PAF antagonists such as



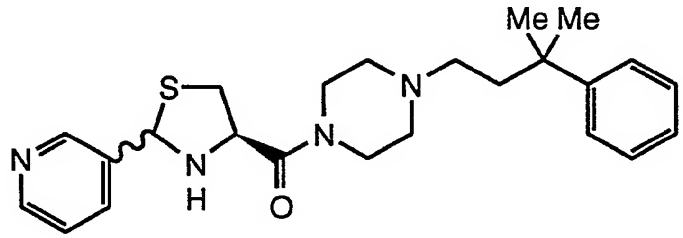
are disclosed in EP-425134-A;

pyridyl PAF antagonists such as



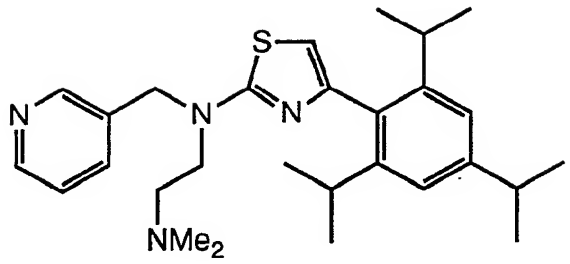
are described by Davidsen et al. (Davidsen, S.K., Summers, J.B., Conway, R.G., Rhein, D.A., Carter, G.W., In Abstacts of the 203rd ACS National Meeting, 5-10 April 1992, San Francisco, CA; American Chemical Society, 1992, Abstract No. Medi 161.);

pyridyl PAF antagonists such as



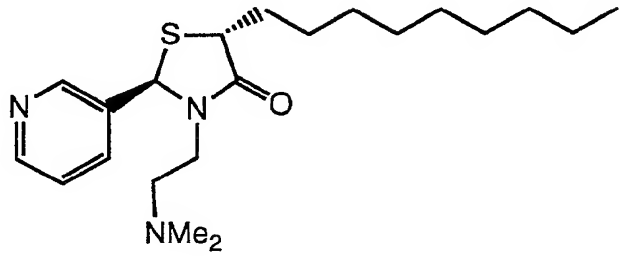
are disclosed in US4987132;

pyridyl PAF antagonists such as



are disclosed in WO9109857; and

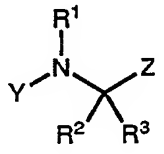
pyridyl PAF antagonists such as



are disclosed in US4992455.

The compounds of the present invention belong to the same class as the compounds described above but differ in that amino acid and amino alcohol derivatives are employed as the "lipophilic" grouping. The present invention provides a range of novel and useful PAF antagonists and their pharmaceutically acceptable acid addition salts, and pharmaceutical uses thereof as PAF antagonists.

According to a first aspect of the invention there is provided a compound of general formula I:



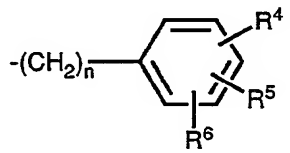
I

wherein:

R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8

cycloalkenyl or phenyl optionally substituted by one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkyl, halogen, -CF_3, -CN;

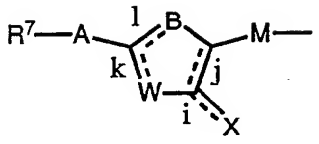
R^2, and R^3 independently represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)S(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)S(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_2-C_6 alkenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, -(C_1-C_6 alkyl)morpholino, -(C_1-C_6 alkyl)OCH_2Ph, -CH_2OSi(C_1-C_6 alkyl)$_3$, -CH_2OSiPh$_2$$C_1$-$C_6$ alkyl or a group -D wherein D represents a group;



wherein n is an integer from 0 to 3, and each of R^4, R^5 and R^6 is independently hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OCH_2Ph, halogen, -CN, -CF_3, -CO_2H, -$CO_2$$C_1$-$C_6$ alkyl, -$CONH_2$, -CONHC_1-C_6 alkyl, -CONH(C_1-C_6 alkyl)$_2$, -CHO, -CH_2OH, -NH_2, -NHCOC_1-C_6 alkyl, -S$O_2$$C_1$-$C_6$ alkyl, or -$SO_2$$C_1$-$C_6$ alkyl;

Y represents a) a hydrogen atom or a -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -$CO_2$$C_1$-$C_6$ alkyl, -($CO_2$$C_1$-$C_6$ alkyl)phenyl, -(C_1-C_6 alkyl)$CO_2$$C_1$-$C_6$ alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or phenyl group, any of which may optionally be substituted by one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkyl, halogen, -CF_3 or -CN; or

b) a -JQ group wherein J is a C=O, C=S, SO_2 or PO_2 group and Q is a group of general formula II:



II

wherein;

k is a single or a double bond;

j is a single or a double bond;

l is a single or a double bond;

i is a single or a double bond;

provided that, when one of k and l is a double bond, the other of k and l is a single bond, and when one of j and i is a double bond, the other of j and i is a single bond;

X represents a =O group when i is a double bond or a $-R^8$ group when i is a single bond;

R^7 represents a 5- or 6-membered aromatic heterocyclic ring containing one or more non-quaternised sp2 nitrogen atoms in its ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, $-C_1-C_4$ perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, $-CONH_2$, -CN, a group -D wherein D is as defined above, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-NHR^9$, $-NR^9R^9$, $-CO_2R^9$ or $-CONHR^9$ wherein R^9 is $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl or C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, $-C_1-C_4$ perfluoroalkyl, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, $-OC_1-C_6$ alkyl, $-SC_1-C_6$ alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

A represents a bond, a -CH_2-, -O-, -S-, -CH_2O-, -CH_2S- or -CH_2NR^{10}- group;

B and W each independently represents a -CR^{11}-, =CR^{11}-, -NR^{11}-, =N-, -O- or -S- group;

each of R^8, R^{10} and R^{11} independently represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, or a group -D wherein D is as defined above;

or R^8 together with R^{11} and the atoms to which they are attached form a 5 to 6 membered oxygen or nitrogen-containing heterocyclic ring;

or R^9 together with R^{11} and the atoms to which they are attached form a 7 membered nitrogen-containing heterocyclic ring optionally substituted by one or more substituents selected from hydrogen, -C_1-C_6 alkyl and a group -D wherein D is as defined above;

M represents a) a bond;

b) a divalent alkanediyl group from 1 to 6 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl and halo;

c) a divalent alkenediyl or alkynediyl group from 2 to 6 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl and halo;

d) a -$(CH_2)_qU(CH_2)_r$- group wherein q is an integer from 0-2, r is an integer from 0-3 and U represents a sulphur atom, an oxygen atom, a phenylene group, a -N(H)- group, a -N(C_1-C_6 alkyl)- group or a -N(C(=O) C_1-C_6 alkyl)- group;

or M together with R^8 and the atoms to which they are attached form a 5 to 6 membered cycloalkyl or nitrogen-containing heterocyclic ring substituted by the -J- group;

Z represents a) a -VR^{12} group wherein V is -C(=O)-, -C(=O)O-, -CH_2O-, -$CH_2OC(=O)$-, -C(=S)-, -$CH_2OC(=O)NH$-, -C(=S)O-, -SO_2- or -CH_2S- and R^{12} is hydrogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

b) a -$CH_2NR^{13}R^{14}$ group or a -$CONR^{13}R^{14}$ group wherein each of R^{13} and R^{14} is independently hydrogen, -C_1-C_{18} alkyl optionally substituted by one or more halogen atoms, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a 5- or 6-membered aromatic heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a -JQ group wherein J and Q are as defined above;

provided that, when one of Y and Z is a -JQ group, the other of Y and Z is other than a -JQ group;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt" or "hydrate" unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one or more double bonds, each of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "OC_1-C_6 alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC_1-C_6 alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, the term "C_4-C_8 cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "N(C_1-C_6 alkyl)2" refers to an amino group substituted with two straight chain or branched hydrocarbon groups each having from one to six carbon atoms. Illustrative of such dialkyl amino groups are N,N-dimethyl amino, N,N-diethyl amino, N,N-dipropyl amino, N,N-diisopropyl amino, N,N-dibutyl amino, N,N-diisobutyl amino, N,N-di-sec-butyl amino, N,N-di-tert-

butyl amino, N,N-dipentyl amino, N,N-dineopentyl amino and N,N-dihexyl amino.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

Preferred compounds include those in which, independently or in any compatible combination:

R^1 represents a hydrogen atom, a -C_1-C_6 alkyl group or a -C_2-C_6 alkenyl group;

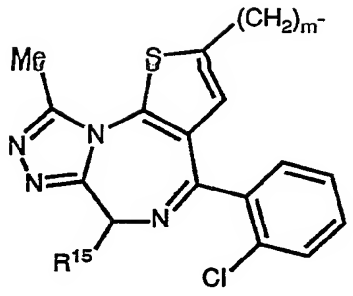
R^2 represents a hydrogen atom;

R^3 represents a -C_1-C_6 alkyl group;

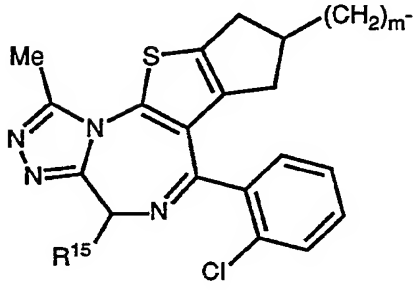
Y represents a -C_1-C_6 alkyl group, a -COC_1-C_6 alkyl group or a -JQ group;

J represents a C=O or SO_2 group;

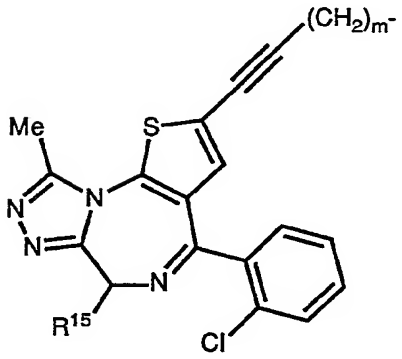
the group of general formula II represents a



group, a



group, a



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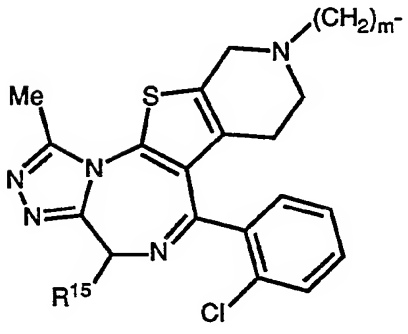

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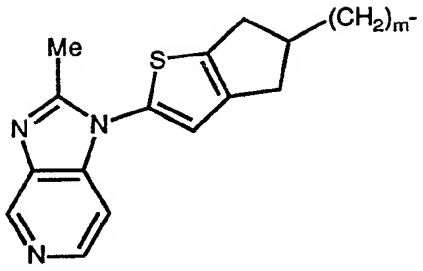

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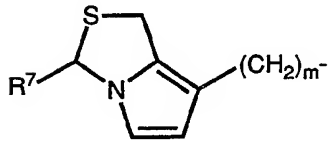

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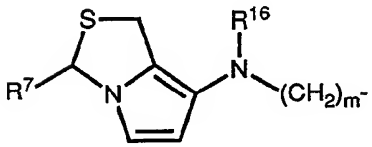

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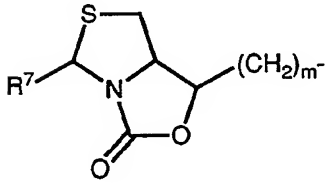

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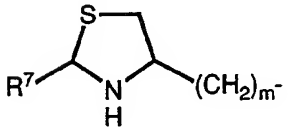

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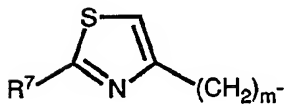

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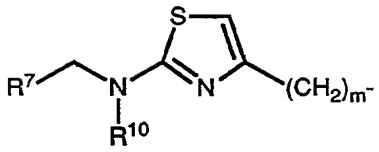
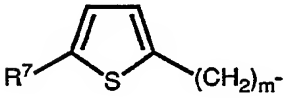
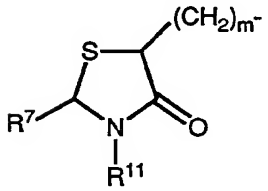


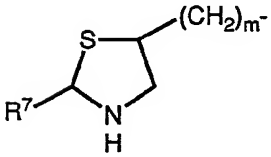
group,



group, a



group, or a



group, wherein R^7, R^{10} and R^{11} are as defined above; R^{15} and R^{16} each independently represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer of 0 to 3;

R^7 represents a 2-methylimidazo[4,5-c]pyrid-l-yl, imidazo-1-yl, benzimidazol-1-yl, 2-methylbenzimidazol-1-yl, 3,5-dimethyl-1,2,4,triazol-4-yl, 2-trifluromethylimidazo[4,5-c]pyrid-1-yl, 2-butylimidazo[4,5-c]pyrid-1-yl, 2-methylimidazo[4,5-b]pyrid-3-yl, 2-methylimidazo[1,2-a]pyrid-3-yl, 2-ethylimidazo[4,5-c]pyrid-1-yl, 7-methoxy-2-methylimidazo[4,5-d]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-5-yl, imidazo[4,5-c]pyrid-l-yl, imidazo[4,5-c]pyrid-3-yl, imidazo[4,5-c]pyrid-5-yl, 2,4,6-trimethoxyimidazo[4,5-c]pyrid-1-yl, 2,4-dimethylimidazol-1-yl, 2-methylimidazol-1-yl, 2,4,5-trimethylimidazol-1-yl, 4-methylimidazol-1-yl, pyrid-3-yl, pyrid-2-yl, 2-methylpyrid-3-yl, 2,6-dimethylpyrid-3-yl, 3,5-

dimethyl-1,2,4-triazol-1-yl, 4-methyloxazol-5-yl, 2,4-dimethylthiazol-5-yl, 6-methylimidazo[1,2-b]thiazol-5-yl, or 4-methylthiazol-5-yl;

R^{10} represents a -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$ group;

Z represents a -VR^{12} group or a -JQ group;

V represents a -C(=O)O- group or a -CH_2O- group;

R^{12} represents a -C_1-C_6 alkyl group.

Exemplary compounds include:

1. N-2-(Pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester,

2. N-5-(Pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester,

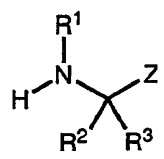
3. N-Methyl-N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester,

4. N-Methyl-N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester.

Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

(a) treating a compound of general formula III



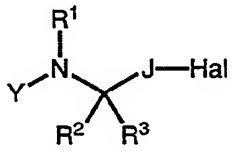
III

wherein R^1, R^2, R^3 and Z are as defined in general formula I, with a compound of general formula IV

Q-J-Hal IV

wherein Q and J are as defined in general formula I and Hal is a halogen such as fluoro, chloro, bromo or iodo, to give a compound of general formula I in which Y is a -JQ group;

(b) treating a compound of general formula V



V

wherein Y, R^1, R^2, R^3 and J are as defined in general formula I, and Hal is a halogen such as fluoro, chloro, bromo or iodo, with a compound of general formula VI

Q-H' VI

wherein Q is as defined in general formula I and H' is a hydrogen atom attached to a nitrogen atom within the Q group, to give a compound of general formula I in which Z is a -JQ group; and

(c) optionally after step (a) or step (b) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

The reaction of step (a) can for preference be conducted in an aprotic solvent, for example tetrahydrofuran, in the presence of a base such as triethylamine, to yield compounds of general formula I.

The reaction of step (b) can for preference be conducted in an aprotic solvent, for example tetrahydrofuran, in the presence of a base such as triethylamine, to yield compounds of general formula I.

By means of step (c) compounds of general formula I wherein Z is a -$CONR^{13}R^{14}$ group wherein R^{13} and R^{14} are as defined in general formula I, may be prepared by the following methods;

i) by treatment of a compound of general formula I wherein Z is a $-CO_2R^{12}$ group wherein R^{12} is a benzyl group with hydrogen in the presence of a noble metal catalyst (eg 10% palladium on charcoal) to give a carboxylic acid which is then treated with an amine of general formula $HNR^{13}R^{14}$ in the presence of a coupling reagent (eg dicyclohexylcarbodiimide;

ii) by treatment of a compound of general formula I wherein Z is a $-CO_2R^{12}$ group wherein R^{12} is a $-C_1$-C_6 alkyl group with a dimethylaluminium amide of general formula IV

$$(Me)_2AlNR^{13}R^{14} \qquad IV$$

wherein R^{13} and R^{14} are as defined in general formula I, which is prepared in situ from trimethylaluminium and an amine of general formula $HNR^{13}R^{14}$.

Also by means of step (c) compounds of general formula I may be prepared by the treatment of a compound of general formula I wherein R^1 is hydrogen with base followed by an electrophile of general formula V

$$LR^1 \qquad V$$

wherein R^1 is as defined in general formula I but is not a hydrogen atom, a phenyl or a substituted phenyl group, and L is a leaving group such as chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy. Electrophiles of general formula V are available in the art or can be prepared by procedures known to those skilled in the art.

Also by means of step (c) certain compounds of general formula I wherein Z is a VR^{12} group wherein V is $-CH_2O-$ and R^{12} is hydrogen may be prepared by treatment of a compound of general formula I wherein Z is a VR^{12} group wherein V is -C(=O)O- and R^{12} is other than hydrogen with a suitable reducing agent (e.g. lithium aluminium hydride).

Also by means of step (c) certain compounds of general formula I wherein Z is a VR^{12} group wherein V is $-CH_2O-$ and R^{12} is other than hydrogen may be prepared by treatment of a compound of general formula I wherein Z is a

VR^{12} group wherein V is $-CH_2O-$ and R^{12} is hydrogen with a suitable base in an aprotic solvent followed by an electrophile of general formula LR^{12} wherein R^{12} is $-C_1-C_6$ alkyl optionally substituted by one or more halogen atoms, $-C_3-C_6$ alkenyl, $-C_3-C_6$ alkynyl, $-(C_1-C_6$ alkyl)OC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)SC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)$O(C_1-C_6$ alkyl)OC_1-C_6 alkyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, pyridyl, a group -D or a $-(C_1-C_6$ alkyl)OD group.

Also by means of a step (c) certain compounds of general formula I wherein Z is a VR^{12} group wherein V is a $-CH_2O(C=O)-$ R^{12} is as defined in general formula I but is not hydrogen, may be prepared by treatment of a compound of general formula I wherein Z is a VR^{12} group wherein V is a $-CH_2O-$ group and R^{12} is hydrogen with a compound of general formula $LC(=O)R^{12}$ wherein L is as defined above and R^{12} is as defined in general formula I but is not hydrogen.

Also by means of a step (c) certain compounds of general formula I wherein Z is a VR^{12} group wherein V is a $-CH_2O(C=O)NH-$, R^{12} is as defined in general formula I but is not hydrogen, may be prepared by treatment of a compound of general formula I wherein Z is a VR^{12} group wherein V is a $-CH_2O-$ group and R^{12} is hydrogen with a compound of general formula $OCNR^{12}$ wherein R^{12} is as defined in general formula I but is not hydrogen.

Compounds of general formula III, IV, V and VI are known in the art or may be prepared by methods analogous to those known in the art.

The appropriate solvents employed in the above reactions are solvents wherein the reactants are soluble but do not react with the reactants. The preferred solvents vary from reaction to reaction and are readily ascertained by one of ordinary skill in the art.

This invention also relates to a method of treatment for patients (or animals including mammalian animals raised in the dairy, meat, or fur trades, or as pets) suffering from disorders or diseases which can be attributed to PAF as previously described, and more specifically, a method of treatment involving the administration of PAF antagonists of general formula I as the active ingredient. In addition to the treatment of warm blooded animals such as mice,

rats, horses, cattle, pigs, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

According to a third aspect of the invention there is provided a compound of general formula I for use in human or veterinary medicine particularly in the management of diseases mediated by PAF; compounds of general formula I can be used among other things to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions.

According to an fourth aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of PAF-mediated diseases, and/or the treatment of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

Compounds of general formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

According to a fifth aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula I and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges,

aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty

acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending

agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of general formula I may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of general formula I may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of general formula I may be used for the treatment of the respiratory tract by nasal or bucal administration of, for example, aerosols or

sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

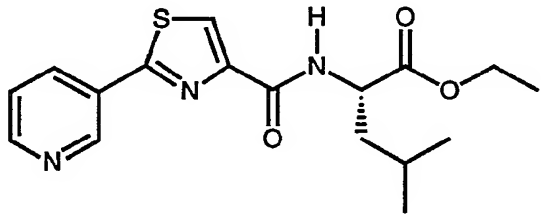
It has been found that the compounds of general formula I exhibit in vitro antagonistic activities with respect to PAF. Compounds of general formula I inhibit PAF-induced functions in both the cellular and tissue levels by changing the PAF binding to its specific receptor site. The ability of compounds of general formula I to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes was measured according to Example 5.

The following examples illustrate the invention, but are not intended to limit the scope in any way.
The following abbreviations have been used in the Examples:-
DCM - Dichloromethane
DIPE - Diisopropylether
THF - Tetrahydrofuran
DMF - N,N-Dimethylformamide

Unless otherwise stated ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using $CDCl_3$ as a solvent and internal reference and are reported as delta ppm from TMS.

Example 1

N-2-(Pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester



A stirred mixture of N-2-(pyrid-3-yl)thiazole-4-carboxylic acid (3.0 g, 14.5 mmol), N-methylmorpholine (1.92 ml, 17.2 mmol) and N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.8 g, 14.6 mmol) in dry DCM was treated with pentafluorophenol (5.4 g, 29.3 mmol) at room temperature. The reaction mixture was stirred for 4 h and a mixture of l-leucine ethyl ester hydrochloride (2.7 g, 13.8 mmol) and triethyl amine (2 ml) in DCM (40 ml) was added. The reaction mixture was stirred overnight at

room temperature and the solvent removed. The residue was taken up in 2N hydrochloric acid and washed with ethyl acetate, basified with 2N sodium hydroxide and extracted into ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous sodium sulphate, filtered and evaporated. The residue was purified by chromatography (silica: ethyl acetate) to give N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester (2.55 g, 50%) as a pale yellow oil.

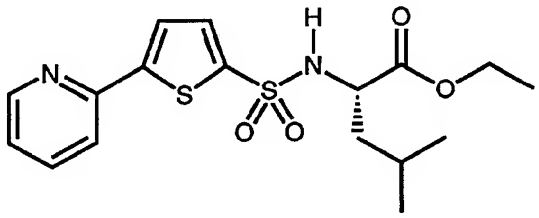
i.r. ($CDCl_3$) 1730, 1665 cm^{-1}

$delta_H$ 9.09 (1H, m), 8.61 (1H, m), 8.18-8.10 (1H, m), 8.09 (1H, s), 7.75 (1H, d, J 8.7 Hz), 7.38-7.28 (1H, m), 4.84-4.70 (1H, m), 4.15 (2H, q, J 7.1 Hz), 1.78-1.60 (3H, m), 1.22 (3H, t, J 7.1 Hz), 0.94 (3H, d, J 6.1 Hz), 0.90 (3H, d, J 5.9 Hz);

$delta_C$ 172.29, 164.30, 160.01, 150.75, 150.37, 147.11, 133.41, 128.37, 123.76, 123.41, 60.94, 50.41, 41.16, 24.53, 22.49, 21.49, 13.77.

Example 2

N-5-(Pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester



A stirred solution of N-5-(pyrid-2-yl)thiophene-2-sulphonyl chloride (5.0 g, 19 mmol) in dry THF (100 ml) was treated with a mixture of L-leucine ethyl ester hydrochloride (7.1 g, 36 mmol) and triethylamine (5.4 ml) in dry THF (50 ml). The reaction mixture was stirred overnight at room temperature and the solvent removed. The residue was taken up in 2N hydrochloric acid and washed with ethyl acetate, basified with 2N sodium hydroxide and extracted into ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous sodium sulphate, filtered and evaporated. The residue was purified by chromatography (silica: 1:1 ethyl acetate/hexane) to give N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester (4.0 g, 55%) as a white amorphous solid.

Analysis calculated for $C_{17}H_{22}N_2O_4S_2$
Requires C 53.38 H 5.80 N 7.32
Found C 53.41 H 5.84 N 7.30

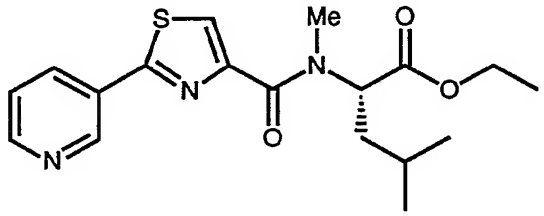
i.r. ($CDCl_3$) 1735, 1350, 1160 cm^{-1}

$delta_H$ 8.58-8.53 (1H, m), 7.78-7.60 (2H, m), 7.54 (1H, d, J 3.9 Hz), 7.45 (1H, d, J 3.9 Hz), 7.28-7.18 (1H, m), 5.45 (1H, d, J 9.8 Hz), 4.11-3.89 (3H, m), 1.92-1.73 (1H, m), 1.58-1.49 (2H, m), 1.09 (3H, t, J 7.2 Hz), 0.94-0.86 (6H, m);

$delta_C$ 172.13, 151.53, 150.72, 149.71, 141.22, 137.43, 132.95, 123.54, 123.36, 119.00, 61.65, 54.71, 42.24, 24.25, 22.67, 21.39, 13.83.

Example 3

N-Methyl-N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester



A stirred solution of N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester (1.69 g, 4.9 mmol) in dry THF (150 ml) was treated with sodium hydride (60% dispersion in oil: 0.21 g, 5.3 mmol) at 0°C under argon. The mixture was allowed to warm up to room temperature and was stirred for 0.5 h. Methyl iodide (0.9 ml, 14.5 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate, washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated. The residue was purified by chromatography (silica: 20% ethyl acetate in hexane) to give N-methyl-N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester (0.6 g, 34%) as a pale yellow oil.

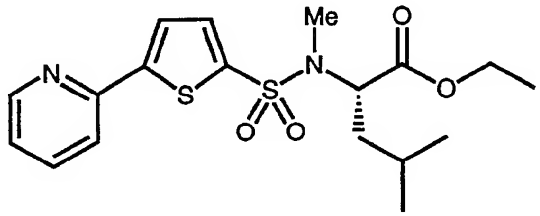
i.r. ($CDCl_3$) 2220, 1730, 1620, 1400, 1020 cm^{-1}

delta$_H$ 9.08 (1H, dd, J 10.7, 1.7 Hz), 8.58 (1H, dd, J 4.8, 1.5 Hz), 8.18-8.05 (1H, m), 7.98 (1H, d, J 5.4 Hz), 7.38-7.26 (1H, m), 5.43 (0.5H, dd, J 10.4, 4.8 Hz), 5.29 (0.5H, dd, J 9.0, 6.4 Hz), 4.22-4.04 (2H, m), 3.22 (1.5H, s), 3.01 (1.5H, s), 1.88-1.42 (3H, m), 1.19 (3H, t, J 7.1 Hz), 0.93 (1.5H, d, J 6.0 Hz), 0.90 (1.5H, d, J 8.9 Hz), 0.84 (1.5H, d, J 6.5 Hz), 0.68 (1.5H, d, J 6.4 Hz);

delta$_C$ 171.68, 171.35, 150.90, 150.82, 147.38, 133.47, 133.41, 125.33, 123.51, 61.00, 60.86, 58.89, 55.44, 38.06, 37.00, 33.44, 29.76, 24.76, 24.55, 23.01, 22.88, 21.33, 21.02, 13.98.

Example 4

N-Methyl-N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester



N-Methyl-N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester was prepared by the procedure of Example 3 employing N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester in lieu of N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester.

Colourless oil (36% yield after chromatography (silica: 35% ethyl acetate in hexane):

Analysis calculated for $C_{18}H_{24}N_2O_4S_2$
Requires C 54.52 H 6.10 N 7.06
Found C 54.55 H 6.16 N 7.10

i.r. ($CDCl_3$) 2210, 1730, 1585, 1420, 1350 cm^{-1}

delta$_H$ 8.52 (1H, d, J 4.9 Hz), 7.74-7.62 (2H, m), 7.48-7.45 (2H, m), 7.25-7.17 (1H, m), 4.66 (1H, t, J 7.6 Hz), 4.00-3.85 (2H, m), 2.92 (3H, s), 1.74-1.57 (3H, m), 1.07 (3H, t, J 7.1 Hz), 0.95 (3H, d, J 4.9 Hz), 0.93 (3H, d, J 5.8 Hz);

delta$_C$ 170.51, 150.85, 150.59, 149.40, 140.02, 136.71, 132.16, 123.22, 123.08, 118.76, 60.79, 57.16, 37.95, 29.77, 24.16, 22.72, 20.90.

Example 5

Inhibition of [^{3}H]-PAF Receptor Binding

The inhibition of [^{3}H]-PAF binding to human platelet plasma membrane by compounds of general formula I was determined by isotopic labelling and filtration techniques. Platelet concentrates were obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) were centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant was subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to pellet the platelets present. The platelet rich pellets were resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll were removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets were resuspended in buffer (10 mM Tris, 5mM $MgCl_2$, 2 mM EDTA, pH 7.0), snap frozen in liquid N_2 and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step was repeated at least 3 times to ensure proper lysis. The lysed platelets were centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step was repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet membranes may be stored at -70°C. After thawing the prepared membranes were centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay was conducted by preparing a series of Tris-buffered solutions of the selected antagonist of predetermined concentrations. Each of these solutions contained [^{3}H]-PAF (0.5 nM; 1-O-[^{3}H]octadecyl-2-acetyl-sn-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10mM Tris, 5mM $MgCl_2$, pH 7.0, 0.25% BSA) to make the final volume 1ml. Incubation was initiated by the addition of 100 µg of the isolated membrane fraction to each of the above solutions at 0°C. Two control

samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, were also prepared and incubated simultaneously with the test samples. After 1 hour incubation, each solution was filtered rapidly under vacuo through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case was rapidly washed 4 times with 5 ml cold (4°C) Tris-buffer solution. Each washed residue was dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as "TB"; and the counts for nonspecific binding from the control sample C2 as "NSB", the percent inhibition of each test antagonist can be determined by the following equation:

%Inhibition = [(TB-TBA)/SB]x100

where the specific binding SB = TB-NSB

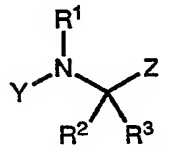
Table 1 lists results from this assay for inhibition of [^{3}H]-PAF receptor binding for illustrative examples of the compounds of this invention.

Table 1: Results for inhibition of [^{3}H]-PAF receptor binding

Example	Inhibition of [^{3}H]-PAF binding IC_{50} nM
1	20
2	30

CLAIMS

1. A compound of general formula I:

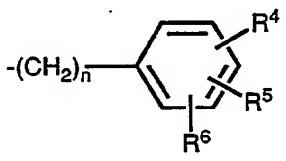


I

wherein:

R^1 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or phenyl optionally substituted by one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkyl, halogen, -CF_3, -CN;

R^2, and R^3 independently represents hydrogen, halogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)S(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)S(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_2-C_6 alkenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, -(C_1-C_6 alkyl)morpholino, -(C_1-C_6 alkyl)OCH_2Ph, -CH_2OSi(C_1-C_6 alkyl)$_3$, -$CH_2OSiPh_2C_1$-C_6 alkyl or a group -D wherein D represents a group;

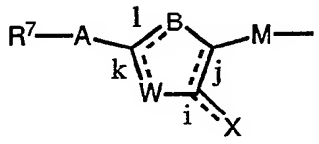


wherein n is an integer from 0 to 3, and each of R^4, R^5 and R^6 is independently hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OCH_2Ph, halogen, -CN, -CF_3, -CO_2H, -CO_2C_1-

C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CONH(C_1$-C_6 alkyl)$_2$, -CHO, -CH_2OH, -NH_2, -$NHCOC_1$-C_6 alkyl, -SOC_1-C_6 alkyl, or -SO_2C_1-C_6 alkyl;

Y represents a) a hydrogen atom or a -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -(CO_2C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or phenyl group, any of which may optionally be substituted by one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkyl, halogen, -CF_3 or -CN; or

b) a -JQ group wherein J is a C=O, C=S, SO_2 or PO_2 group and Q is a group of general formula II:



II

wherein;

k is a single or a double bond;

j is a single or a double bond;

l is a single or a double bond;

i is a single or a double bond;

provided that, when one of k and l is a double bond, the other of k and l is a single bond, and when one of j and i is a double bond, the other of j and i is a single bond;

X represents a =O group when i is a double bond or a -R^8 group when i is a single bond;

R^7 represents a 5- or 6-membered aromatic heterocyclic ring containing one or more non-quaternised sp2 nitrogen atoms in its ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein

at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, -C_1-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -$CONH_2$, -CN, a group -D wherein D is as defined above, -R^9, -OR^9, -SR^9, -SOR^9, -SO_2R^9, -NHR^9, -NR^9R^9, -CO_2R^9 or -$CONHR^9$ wherein R^9 is -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl or C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C_1-C_4 perfluoroalkyl, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

A represents a bond, a -CH_2-, -O-, -S-, -CH_2O-, -CH_2S- or -CH_2NR^{10}- group;

B and W each independently represents a -CR^{11}-, =CR^{11}-, -NR^{11}-, =N-, -O- or -S- group;

each of R^8, R^{10} and R^{11} independently represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, or a group -D wherein D is as defined above;

or R^8 together with R^{11} and the atoms to which they are attached form a 5 to 6 membered oxygen or nitrogen-containing heterocyclic ring;

or R^9 together with R^{11} and the atoms to which they are attached form a 7 membered nitrogen-containing heterocyclic ring optionally substituted by one or more substituents selected from hydrogen, -C_1-C_6 alkyl and a group -D wherein D is as defined above;

M represents a) a bond;

b) a divalent alkanediyl group from 1 to 6 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl and halo;

c) a divalent alkenediyl or alkynediyl group from 2 to 6 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl and halo;

d) a -$(CH_2)_q$U$(CH_2)_r$- group wherein q is an integer from 0-2, r is an integer from 0-3 and U represents a sulphur atom, an oxygen atom, a phenylene group, a -N(H)- group, a -N(C_1-C_6 alkyl)- group or a -N(C(=O) C_1-C_6 alkyl)- group;

or M together with R^8 and the atoms to which they are attached form a 5 to 6 membered cycloalkyl or nitrogen-containing heterocyclic ring substituted by the -J- group;

Z represents a) a -VR^{12} group wherein V is -C(=O)-, -C(=O)O-, -CH_2O-, -CH_2OC(=O)-, -C(=S)-, -CH_2OC(=O)NH-, -C(=S)O-, -SO_2- or -CH_2S- and R^{12} is hydrogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

b) a -CH_2N$R^{13}R^{14}$ group or a -CON$R^{13}R^{14}$ group wherein each of R^{13} and R^{14} is independently hydrogen, -C_1-C_{18} alkyl optionally substituted by one or more halogen atoms, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a 5- or 6-membered aromatic heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a -JQ group wherein J and Q are as defined above;

provided that, when one of Y and Z is a -JQ group, the other of Y and Z is other than a -JQ group;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in Claim 1, wherein R^1 represents a hydrogen atom, a -C_1-C_6 alkyl group or a -C_2-C_6 alkenyl group.

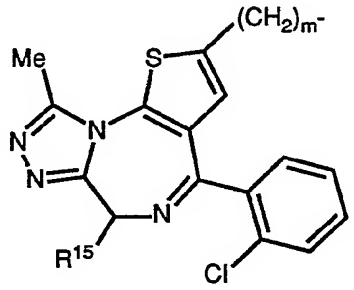
3. A compound as claimed in Claim 1 or 2, wherein R^2 represents a hydrogen atom.

4. A compound as claimed in any one of Claims 1 to 3, wherein R^3 represents a -C_1-C_6 alkyl group.

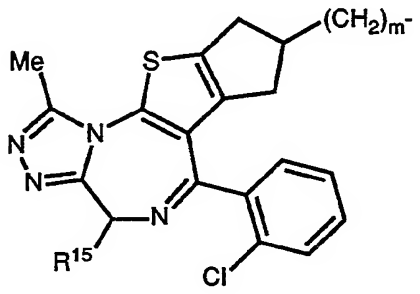
5. A compound as claimed in any one of Claims 1 to 4, wherein Y represents a -C_1-C_6 alkyl group, a -COC_1-C_6 alkyl group or a -JQ group.

6. A compound as claimed in any one of Claims 1 to 5, wherein J represents a C=O or SO_2 group.

7. A compound as claimed in any one of Claims 1 to 6, wherein the group of general formula II represents a



group, a



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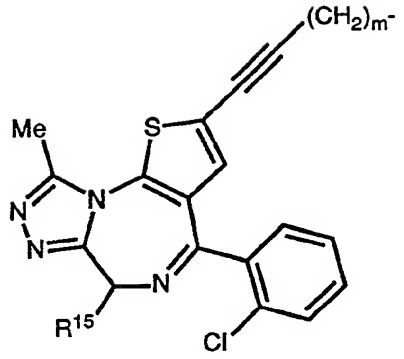

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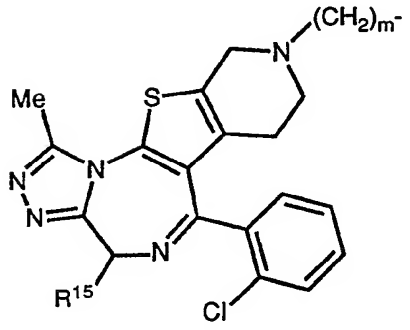
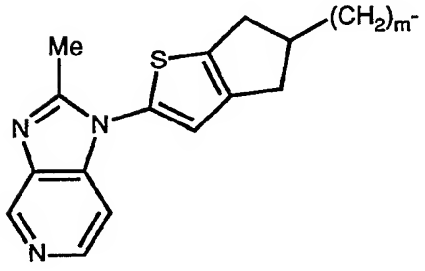


group, a



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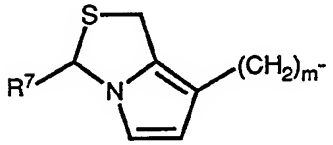

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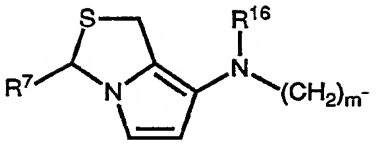

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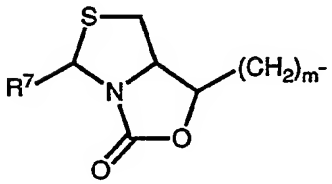

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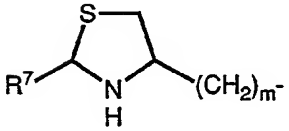

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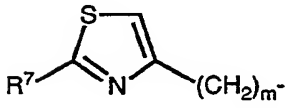

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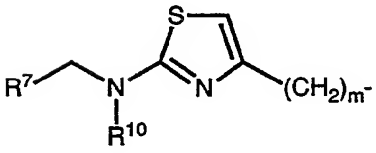
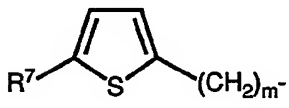
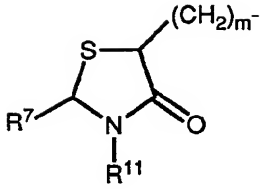


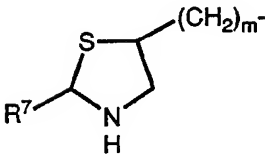
group,



group, a



group, or a



group, wherein R^7, R^{10} and R^{11} are as defined above; R^{15} and R^{16} each independently represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer of 0 to 3.

8. A compound as claimed in any one of Claims 1 to 7, wherein R^7 represents a 2-methylimidazo[4,5-c]pyrid-l-yl, imidazo-1-yl, benzimidazol-1-yl, 2-methylbenzimidazol-1-yl, 3,5-dimethyl-1,2,4,triazol-4-yl, 2-trifluromethylimidazo[4,5-c]pyrid-1-yl, 2-butylimidazo[4,5-c]pyrid-1-yl, 2-methylimidazo[4,5-b]pyrid-3-yl, 2-methylimidazo[1,2-a]pyrid-3-yl, 2-ethylimidazo[4,5-c]pyrid-1-yl, 7-methoxy-2-methylimidazo[4,5-d]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-5-yl, imidazo[4,5-c]pyrid-l-yl, imidazo[4,5-c]pyrid-3-yl, imidazo[4,5-c]pyrid-5-yl, 2,4,6-trimethoxyimidazo[4,5-c]pyrid-1-yl, 2,4-dimethylimidazol-1-yl, 2-methylimidazol-1-yl, 2,4,5-trimethylimidazol-1-yl, 4-methylimidazol-1-yl, pyrid-3-yl, pyrid-2-yl, 2-methylpyrid-3-yl, 2,6-dimethylpyrid-3-yl, 3,5-dimethyl-1,2,4-triazol-1-yl, 4-methyloxazol-5-yl, 2,4-dimethylthiazol-5-yl, 6-methylimidazo[1,2-b]thiazol-5-yl, or 4-methylthiazol-5-yl.

9. A compound as claimed in any one of Claims 1 to 8, wherein R^{10} represents a -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)2 group.

10. A compound as claimed in any one of Claims 1 to 9, wherein Z represents a -VR^{12} group or a -JQ group.

11. A compound as claimed in Claim 10, wherein V represents a -C(=O)O- group or a -CH_2O- group.

12. A compound as claimed in Claim 10 or Claim 11, wherein R^{12} represents a -C_1-C_6 alkyl group.

13. N-2-(Pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester,
N-5-(Pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester,
N-Methyl-N-2-(pyrid-3-yl)thiazole-4-carbonyl-L-leucine ethyl ester,
N-Methyl-N-5-(pyrid-2-yl)thiophene-2-sulphonyl-L-leucine ethyl ester;

or a salt of such a compound.

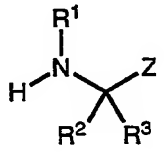
14. A compound as claimed in any one of Claims 1 to 13 for use in human or veterinary medicine, particularly in the management of diseases or conditions mediated by platelet-activating factor.

15. The use of a compound as claimed in any one of Claims 1 to 14 in the preparation of an agent for the treatment or prophylaxis of diseases or conditions mediated by platelet-activating factor.

16. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of Claims 1 to 14 and a pharmaceutically and/or veterinarily acceptable carrier.

17. A process for preparing a compound of general formula I as defined in Claim 1, the process comprising:

(a) treating a compound of general formula III



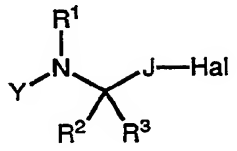
III

wherein R^1, R^2, R^3 and Z are as defined in general formula I, with a compound of general formula IV

Q-J-Hal IV

wherein Q and J are as defined in general formula I and Hal is a halogen such as fluoro, chloro, bromo or iodo, to give a compound of general formula I wherein Y is a -JQ group;

(b) treating a compound of general formula V



V

wherein Y, R^1, R^2, R^3 and J are as defined in general formula I, and Hal is a halogen such as fluoro, chloro, bromo or iodo, with a compound of general formula VI

Q-H' VI

wherein Q is as defined in general formula I and H' is a hydrogen atom attached to a nitrogen atom within the Q group, to give a compound of general formula I wherein Z is a -JQ group; and

(c) optionally after step (a) or step (b) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

c) a divalent alkenediyl or alkynediyl group from 2 to 6 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl and halo;

d) a -$(CH_2)_qU(CH_2)_r$- group wherein q is an integer from 0-2, r is an integer from 0-3 and U represents a sulphur atom, an oxygen atom, a phenylene group, a -N(H)- group, a -N(C_1-C_6 alkyl)- group or a -N(C(=O) C_1-C_6 alkyl)- group;

or M together with R^8 and the atoms to which they are attached form a 5 to 6 membered cycloalkyl or nitrogen-containing heterocyclic ring substituted by the -J- group;

provided that when J is a C=O group, k, l, j and i are single bonds, B is a -NR^{11}- group, W is a -S- group and X is a -R^8 group the group M is other than a bond;

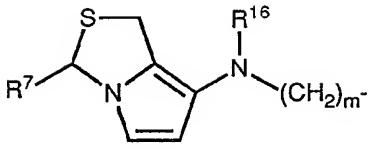
Z represents a) a -VR^{12} group wherein V is -C(=O)-, -C(=O)O-, -CH_2O-, -CH_2OC(=O)-, -C(=S)-, -CH_2OC(=O)NH-, -C(=S)O-, -SO_2- or -CH_2S- and R^{12} is hydrogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

b) a -$CH_2NR^{13}R^{14}$ group or a -$CONR^{13}R^{14}$ group wherein each of R^{13} and R^{14} is independently hydrogen, -C_1-C_{18} alkyl optionally substituted by one or more halogen atoms, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, pyridyl, a group -D as defined above or R^{13} and R^{14} together with the nitrogen atom to which they are attached form an unsubstituted 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a 5- or 6-membered aromatic heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a -JQ group wherein J and Q are as defined above;

provided that, either one of Y or Z is a -JQ group, and that when Y is a -JQ group Z is other than a -JQ group and when Z is a -JQ group Y is other than a -JQ group;



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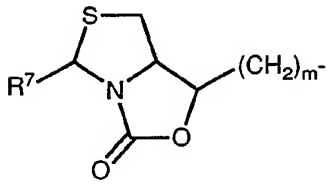

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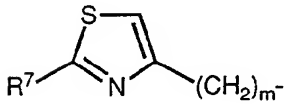

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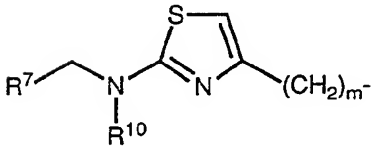

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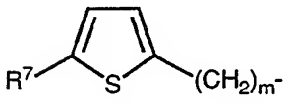

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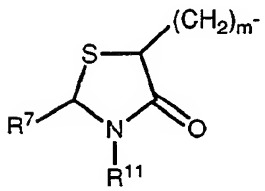
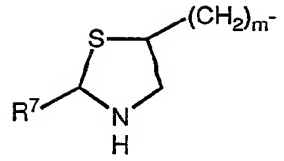
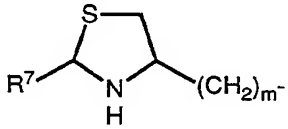


group, or a



group, wherein R^7, R^{10} and R^{11} are as defined above; R^{15} and R^{16} each independently represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer of 0 to 3; or a



group, wherein R^7, R^{10} and R^{11} are as defined above; R^{15} and R^{16} each independently represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer of 1 to 3;

8. A compound as claimed in any one of Claims 1 to 7, wherein R^7 represents a 2-methylimidazo[4,5-c]pyrid-l-yl, imidazo-1-yl, benzimidazol-1-yl, 2-methylbenzimidazol-1-yl, 3,5-dimethyl-1,2,4,triazol-4-yl, 2-trifluromethylimidazo[4,5-c]pyrid-1-yl, 2-butylimidazo[4,5-c]pyrid-1-yl, 2-methylimidazo[4,5-b]pyrid-3-yl, 2-methylimidazo[1,2-a]pyrid-3-yl, 2-ethylimidazo[4,5-c]pyrid-1-yl, 7-methoxy-2-methylimidazo[4,5-d]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-3-yl, 2-methylimidazo[4,5-c]pyrid-5-yl, imidazo[4,5-c]pyrid-l-yl, imidazo[4,5-c]pyrid-3-yl, imidazo[4,5-c]pyrid-5-yl, 2,4,6-trimethoxyimidazo[4,5-c]pyrid-1-yl, 2,4-dimethylimidazol-1-yl, 2-methylimidazol-1-yl, 2,4,5-trimethylimidazol-1-yl, 4-methylimidazol-1-yl, pyrid-3-yl, pyrid-2-yl, 2-methylpyrid-3-yl, 2,6-dimethylpyrid-3-yl, 3,5-dimethyl-1,2,4-triazol-1-yl, 4-methyloxazol-5-yl, 2,4-dimethylthiazol-5-yl, 6-methylimidazo[1,2-b]thiazol-5-yl, or 4-methylthiazol-5-yl.

9. A compound as claimed in any one of Claims 1 to 8, wherein R^{10} represents a -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$ group.

10. A compound as claimed in any one of Claims 1 to 9, wherein Z represents a -VR^{12} group or a -JQ group.

11. A compound as claimed in Claim 10, wherein V represents a -C(=O)O- group or a -CH_2O- group.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
GB 9226370.6

Relevant Technical fields

(i) UK Cl (Edition 1) C2C (CKK, CSJ)

(ii) Int Cl (Edition 5) C07D

Search Examiner
S J QUICK

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: CAS ONLINE

Date of Search
9 FEBRUARY 1993

Documents considered relevant following a search in respect of claims 1-17

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	US 4992455 (SUMITOMO) 12 February 1991, see page 5 (2nd formula) of this application: compound of formula I, Y=R^1=Me, R^2=R^3=H, Z=CH_2-$NR^{13}R^{14}$ $NR^{13}R^{14}$ is 5-8m N containing hetrocycle	1-3,5 & 14-16 at least
X	US 4987132 (YAMANOUCHI PHARM.) 22 January 1991, see N-[[2-(3-pyridyl)-4-thia-zolidinyl] carbonyl glycine methyl ester and the corresponding compounds with an Et and i-Bu amino acid side chain.	1 & 14-16 at least
X	Glycine, alanine, valine & leucine	1

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

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E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

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